

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/00, 47/32	A1	(11) International Publication Number: WO 96/10989 (43) International Publication Date: 18 April 1996 (18.04.96)
(21) International Application Number: PCT/US95/13424 (22) International Filing Date: 6 October 1995 (06.10.95) (30) Priority Data: 08/319,495 7 October 1994 (07.10.94) US (71)(72) Applicants and Inventors: BOLOGNA, William, Joseph [US/US]; 501 East 79th Street, New York, NY 10021 (US). LEVINE, Howard, Leslie [US/US]; 15 Franklin Place, Oceanside, NY 11572 (US). (74) Agents: BLACKMAN, Scott, H. et al.; Weil, Gotshal & Manges, 767 Fifth Avenue, New York, NY 10153 (US).		(81) Designated States: AM, AU, BR, BY, CA, FI, GE, HU, JP, KG, KR, KZ, LT, LV, MD, NO, NZ, RU, SI, SK, TJ, UA, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: USE AND COMPOSITION OF AN ANTI-SEXUALLY TRANSMITTED DISEASES FORMULATION (57) Abstract The present invention provides a composition and use of a composition comprising a bioadhesive cross-linked polycarboxylic acid polymer formulation that enables the use of relatively low amounts of anti-STD agents such as N-9, to be used to prevent infection by STDs without causing the irritation to genital tissue that often accompanies higher doses of anti-STDs. The bioadhesive polymer maintains greater contact between the anti-STD agent and the infectant for a much greater period of time, enabling a lower concentration to act longer on the infectant, when compared to currently-available commercial applications containing N-9. Such delivery will enable a safe and non-irritating decrease in the risk of infection with STDs, including HIV.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

USE AND COMPOSITION OF AN ANTI-SEXUALLY TRANSMITTED DISEASES FORMULATION

INTRODUCTION

5 Field of the Invention

This invention relates to a bioadhesive polymer formulation for providing prolonged effect by relatively small concentrations of anti-STD agents, wherein the formulation comprises at least a cross-linked polycarboxylic acid polymer and an anti-STD agent.

10 Background

Human Immunodeficiency Virus (HIV) is presumably the etiologic agent of Acquired Immunodeficiency Syndrome (AIDS). Many attempts have been and continue to be made to find mechanisms and agents to prevent or to cure an HIV infection, without much success.

15 Attention has been focused in part on measures that prevent infection by the virus. One method aimed at the heterosexual population has been the vaginal application of agents prior to and during intercourse, which agents are intended to inactivate the virus or remove its infectivity. An example is the use of surfactant- or detergent-based spermicides, exemplified by nonoxynol-9 ("N-9"), which have demonstrated activity against HIV and
20 other sexually-transmitted diseases (STDs) at concentrations that would be expected to exist during intercourse after pre-coital application of the spermicide to the vagina. However, it is not necessarily a requirement that there be simultaneous presence of anti-STD and spermicidal activity. Currently available formulations of N-9 include jellies and sponges for spermicidal use in the vagina. However, at concentrations which may be effective in
25 reducing the rate of gonococcal and chlamydial cervical infections, the rate of symptomatic irritation of the vagina and/or penis is substantially increased. In a study on the efficacy of

the N-9 contraceptive sponge in preventing sexual acquisition of HIV by highly exposed women, N-9 was not effective in reducing infection by HIV, but genital ulcers and vulvitis occurred with substantially increased frequency.

5 It therefore is of interest to use delivery systems for anti-STDs that maintain contact between the anti-STD and the infective agent without harming host or partner tissue.

Relevant Literature

N-9 has been shown to be effective at inhibiting several sexually transmitted diseases, including AIDS, gonorrhea, chlamydia and trichomonal infections, syphilis and genital herpes. See, e.g., Niruthisard, S., et al., Lancet, 339: 1371 (1992).

10 Vaginal application of a commercially available contraceptive jelly containing 5% N-9 has been shown to be effective in preventing vaginal transmission of herpes simplex virus type 2 (HSV-2) infections in mice. Whaley, K. J., et al., J. Infect. Diseases, 168:1009, 1010-11 (1993). Dextran and the carageen types of polysaccharides have been shown to have an anti-HIV potential. See, e.g., Pearce-Pratt, R. et al., Bio. Reprod., 48:
15 431, 432 (1993).

The efficacy of a formulation based on a cross-linked polycarboxylic acid polymer for moisturization of skin or mucous membranes, such as vaginal tissue, is described in Robinson, J. R., European Patent Applications Serial Nos. 90300327.5 and 90300340.8.

20

SUMMARY OF THE INVENTION

The present invention is related to a method and drug delivery formulation for administration of anti-STD agents at a therapeutic concentration without substantial effect on host tissue, by potentiating the activity of the anti-STD and thereby facilitating its application in a substantially lower concentration. The invention is based upon use of a formulation
25 which includes a bioadhesive cross-linked polycarboxylic acid polymer to deliver an anti-STD agent locally to a mucosal surface of potential exposure to an STD infectant, most

typically a mucosal surface in a host body cavity such as the vagina or rectum. The method finds use in the prevention of infection of the host by STD agents.

BRIEF DESCRIPTION OF THE DRAWING

FIGURE 1 illustrates the comparative virucidal effects, *in vitro*, of N-9 alone and a formulation which includes N-9 and polycarbophil (F-Po/N9), as described in further detail at Example 1. This log graph clearly demonstrates the potentiation of the antiviral effects of N-9 by the present invention, as measured by the reduction in the number of syncytia produced. As illustrated by Figure 1, nonoxynol-9 alone, at concentrations of 1 and 0.1 $\mu\text{g/ml}$, reduced viral infection to 36% and 72% of that otherwise exhibited by the HIV viral suspension described below in Example 1. However, when the virus was contacted instead by F-Po/N9, the N-9 concentrations of only 0.35 and .035 $\mu\text{g/ml}$ limited the viral infection to 23% and 47% of the HIV viral suspension. In Figure 1, the data points for N-9 are represented by squares, and the data points for F-Po/N9 are represented by triangles.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises the use of a drug formulation based upon a delivery agent formulation comprising a cross-linked polycarboxylic acid polymer and an anti-STD agent, to deliver the anti-STD, for example N-9, to mucosal surfaces, particularly in a body cavity, to provide local concentrations of any anti-STD which are sufficient to inhibit or prevent infection by an STD, while substantially decreasing local tissue irritation and side effects often associated with formulations of anti-STD agents.

The use of a cross-linked polycarboxylic acid polymer in combination with an anti-STD agent offers several advantages over use of the anti-STD agent alone. Such polymers potentiate the anti-STD effect of the anti-STD by maintaining contact with the host body cavity tissue and infected tissues or cells, and thus prolonging the interaction between the anti-infectant component and the infectant for a greater time. As a result, a lower concentration of the STD component can be used to achieve anti-infectant activity. At such a lower concentration, the degree and amount of side effects and epithelial irritation caused

by the anti-STD agent is substantially reduced. The bioadhesive polymeric system has the advantage of being held in a body cavity such as the vagina for relatively long periods of time, i.e., as much as 48 to 72 hours or longer, whereas most drug delivery systems are sloughed off the vaginal walls in less than four hours. The polymer holds the anti-infectant agent and slowly releases it over time. The drug delivery system allows for direct contact with any sperm and/or infectant introduced through sexual intercourse, or present in the vaginal or penile secretions prior to intercourse. The delivery system can deliver sufficient anti-infectant to effectively reduce the chance of infection with substantially lower frequency of counter-productive irritation to the genital tissues.

The decrease in the irritation to body cavity mucosal surfaces or to other epithelial tissue encourages more faithful use of the agent resulting in a more effective prevention of STD and/or pregnancy. Unlike most products, which are based on lubricants, the base formulation of the present invention is a moisturizer, further promoting comfort. Also, the effective use of lower concentrations enables a lower amount of N-9 to be used per dose. Another benefit of the present invention is that its compositions may be fabricated with relative ease. Yet another benefit of the present invention is that its compositions may be easily administered without requiring any sponge or other device which must be physically inserted and left in place, and then removed from the site of activity at some later time. A smaller quantity of the formulation is needed, facilitating neater application with less chance of leakage and increased compliance of proper application. Another benefit of the present invention is that it allows the user to apply the product more than just a few minutes before sexual intercourse without significant loss of efficacy of the formulation, further promoting increased compliance.

The polymer used in the drug delivery formulation is a cross-linked polycarboxylic acid polymer wherein at least eighty percent of the monomers of which the polymer is comprised contain at least one carboxyl functionality. The cross-linking agent should be present at such an amount as to provide enough bioadhesion to allow the system to remain attached to the target epithelial surfaces for preferably a period of twenty-four to forty-eight hours. Such results may be measured clinically over various periods of time, by

testing samples of the vaginal vault for concentration of the anti-STD agent or for pH reduction due to the continued presence of the polymer, or both.

This level of bioadhesion is usually attained when the cross-linking agent is present at about 0.1 to 6.0 weight percent of the polymer, with about 1.0 to 2.0 weight percent being preferred, as long as the appropriate level of bioadhesion results. Bioadhesion can also be measured by commercially available surface tensiometers utilized to measure adhesive strength. Suitable cross-linking agents include divinyl glycol, divinylbenzene, N,N-diallylacrylamide, 3,4-dihydroxy-1,5-hexadiene, 2,5-dimethyl-1,5-hexadiene and similar agents.

The basic drug delivery system formulation of the present invention -- the cross-linked polycarboxylic acid polymer formulation to which is added the anti-STD agent -- is generally described in U.S. Patent No. 4,615,697 to Robinson (hereinafter "the '697 patent"), which is incorporated herein by reference. A preferred polymer for use herein is Polycarbophil, U.S.P., which is commercially available from B.F. Goodrich Specialty Polymers of Cleveland, OH under the trade name NOVEON®-AA1. The United States Pharmacopeia, 1995 edition, United States Pharmacopeial Convention, Inc., Rockville, Maryland, at pages 1240-41, indicates that polycarbophil is a polyacrylic acid, cross-linked with divinyl glycol.

Other useful bioadhesive polymers that may be used in the present invention are mentioned in the '697 patent. For example, these include polyacrylic acid polymers cross-linked with, for example, 3,4-dihydroxy-1,5-hexadiene, and polymethacrylic acid polymers cross-linked with, for example, divinyl benzene.

These polymers should not be used in their salt form because this would decrease their bioadhesive capability. Such bioadhesive polymers may be prepared by conventional free radical polymerization techniques utilizing initiators such as benzoyl peroxide, azobisisobutyronitrile, and the like. Exemplary preparations of useful bioadhesives are provided in the '697 patent.

Additionally, the additives taught in the '697 patent may be mixed in with the cross-linked polymer in the formulation for maximum efficacy of the drug delivery system or

for the comfort of the patient. Such additives include, for example, lubricants, plasticizing agents, preservatives, gel formers, binders, vehicles, coloring agents, taste and/or odor controlling agents, humectants, viscosity controlling agents and similar agents, and preferably have no substantial detrimental effect on the anti-STD and/or spermicide activity of the drug delivery formulation.

STD's that can be treated by N-9 include, but are not limited to, AIDS, gonorrhea, chlamydia and trichomonal infections, syphilis and genital herpes. Other anti-STD agents include, for example: other detergents/surfactants, such as octoxynol-9, chlorhexidine, and benzalkonium chloride, which are also generally effective against STDs; and anti-metabolites, such as AZT, or competitive binding inhibitors such as dextrans, all of which are generally most effective against viral STDs, such as HIV and genital herpes.

The anti-STD is mixed into the formulation, associating reversibly with the polymer. Upon application, the anti-STD leaches out of the formulation slowly over time, depending on the proportions and concentrations of the formulation components. Correct concentrations for particular STDs can be determined by testing and comparing the results of various concentrations of an anti-STD against a particular STD, in tests similar to those described below in Example 2.

An exemplary preparation of 50 Kg of F-Po/N9 is as follows:

	INGREDIENT	AMOUNT (Kg)
20	Nonoxynol-9	1.750
	Methylparaben	0.090
	Sorbic Acid	0.040
	Carbomer 934P	0.250
	Polycarbophil	0.500
25	Glycerin	5.000
	Mineral Oil	2.500
	Hydrogenated Palm Oil	
	Glyceride	0.500
	Sodium Hydroxide	0.0125
30	Purified Water	39.3575

Methylparaben and sorbic acid are preservatives, which may be substituted by any other approved preservative, such as benzoic acid or propionic acid.

Carbomer 934P is a gel former, which may be substituted by other gel formers including, but not limited to, carbomer 974, carbomer 980, methylcellulose or propylcellulose.

Glycerin is a humectant; alternative humectants include, for example, propylene glycol or dipropylene glycol.

Mineral oil and hydrogenated palm oil glyceride are lubricating agents; alternatives include, for example, any mineral oil or vegetable oil, such as canola oil, palm oil or light mineral oil.

Sodium hydroxide is simply a strong base for purposes of controlling the pH level; other bases commonly used for that purpose may be substituted.

General preparation involves hydration of the polymers, separate mixing of water-soluble ingredients (the "polymer phase") and oil-soluble ingredients (the "oil phase"), heating and mixing of the two phases, and homogenization of the mixture. All ingredients in this example are well known and readily available from suppliers known in the industry.

As an example, the polymer phase is prepared by dissolving the sorbic acid and methylparaben in purified water (along with about a 3% overage for evaporation losses), preferably at 75-78° C. The solution is cooled, generally to room temperature, and the polycarbophil and Carbomer 934P are added. The polymers are hydrated by mixing for several hours, generally about 2-3 hours until a uniform, smooth, lump-free gel-like polymer mixture is obtained. When the polymers are completely hydrated, the nonoxynol-9 is added and mixed in, until uniform preparation is obtained.

The oil phase is generally prepared by melting together the hydrogenated palm oil glyceride, glycerin and mineral oil. The mixture is cooled to about 60° C., while the polymer phase is warmed to about the same temperature.

The oil phase is then added to the polymer phase, and the two phases are mixed thoroughly, producing a uniform, creamy white product. Mix in sodium hydroxide to produce a pH of about 2.5 - 4.5, generally about 4. When the mixture has cooled, it is de-

aerated. The resulting product is aseptic, because of the nature of the preparation and pH as well as the presence of preservatives.

As will be apparent to those skilled in the art, the composition of the formulation can be varied to control the effectiveness of a particular concentration of anti-STD agent. For example, the concentration of the bioadhesive polymer can be adjusted to provide greater or lesser bioadhesion. The viscosity of the gel can be varied by varying the pH or by changing the concentration of the polymer or gel former. The relative concentrations of the oils compared to the water can be varied to modulate the release rate of the anti-STD from the drug delivery system. The pH can also be varied to affect the release rate or bioadhesiveness of the formulation.

The drug delivery system may be delivered to the body cavity such as vagina or rectum in a variety of fashions as are known in the art, e.g., plunger, douche, suppository or manually. A preferred method of delivery is using the device described in U.S. design patent no. D345,211, which disclosure is incorporated herein by reference. This device is an oblong hollow container, with one end capable of being opened and the other end containing most of the composition to be delivered and capable of being squeezed. Such devices allow for pre-measurement of the amounts of polymer and drug to be delivered in a sealed container which may be used relatively easily. The containers also maintain the drug and polymer in a sterile environment until use. Upon use the container is opened and the open end is inserted into the body cavity by the host or his/her partner, while the other end is squeezed to expel the contents of the container into the body cavity. Accordingly, F-Po/N9 is preferably provided as a kit, which includes at least one single dose delivery device. The kit can include a single dose or multiple doses of the formulation.

In a preferred formulation, F-Po/N9 is prepared using polycarbophil, U.S.P., purchased from B.F. Goodrich Specialty Polymers, as the polymer in about a 1% gel formulation which is adjusted to a pH of about 2.5 - 4.5 with, for example, sodium hydroxide, yielding a viscosity of 40,000 to 90,000 cps. The anti-STD agent is N-9, preferably added at about 2 to 5 weight-percent, and optimally at about 3.5 weight-percent, of the total composition. The dosage of such composition would be preferably about 1 to

about 2.5 g., most preferably about 1.5 g., total weight of formulation, calculated in combination with the concentration of N-9 to yield preferably about 50 to 55 mg, and most preferably about 52.5 mg., of N-9 per dosage. Ideally, the subject should apply one dosage before each act of sexual intercourse, primarily to reinforce faithful use of the formulation at an appropriate frequency. The applicator used is preferably disposable and provides accurate amount of delivery, such as the applicators described in U.S. design patent no. D345,211 and U.S. design patent application serial no. 29/019,916, providing delivery of the desired dosage of formulation at at least about $\pm 5\%$ accuracy.

The examples described and discussed herein are intended to be illustrative of the present invention but not limiting. Numerous variations and modifications may be effected without departing from the true spirit and scope of the novel concepts of the present invention.

EXAMPLES

Example 1 - Comparison of Effects of N-9, Polycarbophil Formulation and Polycarbophil Formulation With N-9 on Viral Suspension of HIV LAV1 BRU Clone

Nonoxynol-9, a 2% polycarbophil formulation (F-Po) and a formulation with about 3.5 % N-9 and about 1% polycarbophil (F-Po/N9) were tested for activity on HT4LacZ cellular infection by a HIV LAV1 BRU retrovirus clone. The formulations were prepared according to the description discussed above, except that the F-Po was prepared with about 2% polycarbophil, no N-9 and about a 1% concentration of Carbomer 934P, rather than 0.5%, and the difference (2%) was made up with additional water.

A viral blank was used as control, and AZT was used for a positive control. Each formulation was set up as an aqueous suspension of a particular concentration. 500 μ l. aliquots of viral suspension were separately mixed with 50 μ l. of each of the test solutions. After 30 minutes, 55 μ l. of each of these mixtures were tested directly on HT4LacZ cells in a well also containing DEAE dextran. During the culturing period, the virus supplies the *tat* gene missing in HT4LacZ cells, leading to LacZ gene transactivation coding for β -galactosidase, indicated by a histochemical coloration. After 72 hours of culturing, infection

is stopped by addition of a fixator for ten minutes. After two PBS washes, the colorant is added for ninety minutes. After syncytia (giant multi-nucleated cells, formed by many cells fusing together when infected with HIV) outbreak, the colorant is replaced with water. Observation is performed with an optical microscope, yielding the following results in Table

5 1:

Table 1. ANTI-HIV ACTIVITY OF F-PO/N9, F-PO AND N-9

Substance	Final Conc. ($\mu\text{g/ml}$)	Syncytia per well; 2 - 4 wells	Total # Syncytia	Avg. # Syncytia per well	Percent Reduction
Viral Reference	-	16, 15, 17	48	16	ϕ
N-9	1.0	6, 5, 7, 5	23	5.75	64
N-9	0.10	12, 11, 13, 10	46	11.5	28
F-Po/N9	0.35	4, 3, 4, 4	15	3.75	77
F-Po/N9	0.035	8, 7, 9, 6	30	7.5	53
F-Po	200	13, -, 11, -	24	12	25
AZT	(10^{-3}M)	0, 0, 0, 0	0	0	100

10

15

20

In Table 1, ϕ percent reduction corresponds to 100% infection by the reference virus, and 100% reduction to the total lack of syncytia in wells for a given formulation. While the control positive AZT demonstrated 100% effectiveness against the virus (0 syncytia produced), the viral reference produced an average of 16 syncytia per well. N-9 alone, at final concentrations of 0.1 and 1 $\mu\text{g/ml}$, respectively, provided 28% and 64% effectiveness

against infection as measured by decreases of syncytia produced. In comparison, F-Po/N9, at final N-9 concentrations of only 0.35 and .035 $\mu\text{g/ml}$, produced 77% and 53% effectiveness against infection, respectively. F-Po, at a final polycarbophil concentration of 200 $\mu\text{g/ml}$, yielded a 25% decrease in infection rate. Clearly, the N-9 in the polycarbophil formulation with N-9 exhibited substantially greater concentration-effectiveness than N-9 alone, as illustrated by Figure 1.

Example 2 - Comparison of Anti-HIV Activity of F-Po/N9 and F-Po

Anti-HIV effects were compared for F-Po/N9 and F-Po, the same formulations as in Example 1 above. This study used increase in p24 core protein from MT2 cells, in cell culture fluid using ELISA, as an indication of viral replication.

To evaluate the effect of F-Po/N9 on HIV replication, samples of virally-exposed MT2 cell culture fluid were serially diluted and tested for increase in p24 antigen. The absorbance for each dilution of virus was plotted, and the 50% endpoint calculated. In this study, the 50% endpoint is the dilution of virus which would give an absorbance of 1.000 at 450 nm. wavelength.

The viral inoculum, using HIV-IIIB produced by co-cultivation of cell lines CEM and CEMCBL1, was mixed with an equal volume of the formulations for 1 minute at room temperature. Then, the mixture was added to 800 μl of isotonic acetate buffer, at a 1:10 dilution. 100 μl of this mixture was then added to 2×10^6 cells in a small tissue culture flask. If necessitated by the concentration, the mixture is diluted before inoculating the cells, to reduce the final concentration of the products in contact with the cells to less than 1 $\mu\text{g/ml}$. As a control, virus was mixed with buffer, held for one minute, and similarly diluted. After 1 hour of incubation at 37°C to allow the virus to adsorb to the cells and for infection to occur, fresh tissue culture medium was added to the flask to bring the volume to 11 ml. The contents were gently mixed, and 1 ml of cell culture removed and titrated for infectious virus, using the microtitre test, and then stored at -20°C until testing for p24 antigen. The flask was then incubated at 37°C for up to 14 days, during which time 1 ml samples of cell culture fluid were removed, titrated and stored for p24 testing.

All samples were tested for p24 antigen by an indirect ELISA, to measure viral replication with time. Inactivated virus would demonstrate a constant level of p24 antigen, indicative of no replication taking place.

5 F-Po reduced the amount of HIV replication by about a third, at polycarbophil concentrations ranging from 2.0 mg/ml to 0.0002 mg/ml. F-Po/N9 almost totally inactivated HIV replication at a concentration of 100 mg/ml (3.5 mg/ml of N-9), and reduced HIV replication by about a third at concentrations of 0.10 to 10 mg/ml (0.0035 to 0.35 mg/ml of N-9), and by under 20% at a concentration of 0.01 mg/ml (0.00035 mg/ml. of N-9).

10 Example 3 - Irritation and Convenience Clinical Trials For Polycarbophil Formulation with N-9

F-Po/N9, as formulated above with about 52.5 mg. per application, was compared to the Today® sponge, a commercial contraceptive sponge product with 1 g. of nonoxynol-9 per application, and Conceptrol®, a commercial vaginal contraceptive gel product containing 100 mg. per application of nonoxynol-9. In this study, one application 15 was made each day by each of 31 female subjects, for seven days consecutively for each product, with a 21-day "washout" period in between products. Each application of the sponge product was left in place for 24 hours.

Blood samples were taken at various times to measure serum concentration of N-9. None of the products produced any significant serum concentrations for any of the 20 subjects. Examinations were also conducted by an investigator to note the existence and degree of any vaginal or cervical irritation, including redness, petechiae, ulceration, infection, punctation, mosaic, leukoplakia, nonstaining squamous epithelium, columnar epithelium or white epithelium. A significantly higher average incidence of irritation was observed with Conceptrol® than with F-Po/N9, and a significantly higher intensity of 25 irritation was observed with the Today® sponge than with F-Po/N9.

In a separate study, subjective comments regarding relative irritation and discomfort were solicited from nineteen female subjects using, at different times, F-Po/N9 and the Today® sponge. Overall preference of one product over the other was also

requested, from 18 of the subjects. The products were used daily for a period of ten days each. F-Po/N9 has a unit dosage of about 52.5 mg. of N-9, while the Today® sponge product contains a unit dosages of 1 g. of N-9. F-Po/N9 generally was preferred by the subjects over the sponge product.

5 In order to demonstrate anti-STD effectiveness of the present invention in vivo for identification or concentration of particular anti-STD agents or particular STD's, clinical studies could be undertaken, for example, in a manner similar to those conducted and described in Kreiss, J., et al., J.A.M.A., 268(4):477-82 (1992) and Niruthisard, S., et al., Lancet, 339: 1371-75 (1992). In each of these studies, previously-uninfected subjects used
10 nonoxynol-9 in one form and formulation or another, over a period of time during and after which they were carefully monitored for compliance of application and for various STDs. The disclosures of these reported studies are incorporated herein by reference; variations on these studies for use with particular parameters will be obvious to those skilled in the art.

 For example, F-Po/N9 as formulated above or otherwise could be
15 administered on a daily basis to a test population, in parallel to a control blank, after thorough initial screening for non-infected individuals. Careful monitoring and testing will disclose the relative infection rate for a particular STD, and thus the effectiveness of that particular formulation of F-Po/N9.

 N-9 is one substance that has been demonstrated to neutralize HIV and
20 lymphocytes containing HIV. However, it is generally used at concentrations so great -- usually 100 - 400 mg. per application, and as much as 1 g. per application -- as to cause a substantial degree and number of side effects, including, at times, cellular lysis of host cells. Such injury may result in an increased susceptibility to infection, in effect counteracting at least in whole or part the anti-infectant activity of the N-9. The present invention should
25 allow, for example, the use of a product containing only about 52.5 g of nonoxynol-9, in a formulation using polycarbophil as the polymer, without compromising the protection afforded by N-9 against infection with HIV and other STDs, or the effectiveness of the preparation as a spermicide. Further, the polymer itself also demonstrates anti-HIV activity. This may be based on the demonstrated ability of polyanions to inhibit the attachment of the

HIV to susceptible cells, presumably by an electrostatic screening. It is thus clear that the present invention provides a formulation which potentiates the anti-HIV activity of N-9.

5 All publications and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

10 The invention now having been fully described, it will be apparent to those skilled in the art that many variations and modifications can be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is:

1. A composition which comprises a bioadhesive cross-linked polycarboxylic acid polymer and an anti-STD agent.
2. A composition according to claim 1 wherein the polymer is polycarbophil.
- 5 3. A composition according to claim 1 or 2 which comprises from 0.1 to 6 weight percent of polymer.
4. A composition according to any one of claims 1 to 3 which further includes sodium hydroxide in an amount which provides a pH of from 2.5 to 4.5.
5. A composition which comprises:
 - 10 a. an anti-STD agent;
 - b. 1 to 2 weight percent of a bioadhesive cross-linked polycarboxylic acid polymer;
 - c. a gel forming agent;
 - d. a humectant; and
 - 15 e. a lubricating agent;optionally containing one or more preservatives, adjuvants, acids or alkalis.
6. A composition according to any one of claims 1 to 5 in unit-dosage form.
7. A composition according to claim 6 wherein the dosage comprises from 50 to 55 mg of the anti-STD agent.
- 20 8. A composition according to any one of claims 1 to 7 wherein the anti-STD agent is nonoxynol-9.
9. A composition which comprises:
 - a. 2 to 5 weight percent of an anti-STD agent;
 - b. 1 to 2 weight percent of a bioadhesive cross-linked polycarboxylic acid
 - 25 polymer;optionally containing one or more preservatives, additives, acids or alkalis.
10. A composition according to any one of claims 1 to 9 for use in a method of preventing or reducing the chances of transmission of or infection by a sexually transmitted disease.

11. A composition for use according to claim 10 wherein the STD is AIDS.
12. Use of from 1 to 2 weight percent of a bioadhesive cross-linked polycarboxylic acid polymer and an anti-STD agent for the manufacture of a medicament for preventing or reducing the chances of transmission of or infection by a sexually transmitted disease.
13. A drug delivery composition comprising a bioadhesive cross-linked polycarboxylic acid polymer formulation with an amount of an anti-STD agent sufficient, upon delivery to a body cavity, to demonstrate anti-STD activity without significant causation of irritation to the local epithelial tissues.
14. A composition according to claim 13 wherein the polymer is polycarbophil.
15. A composition according to claim 13 wherein the composition additionally comprises at least one adjuvant.
16. A composition according to claim 13 wherein the anti-STD agent is an anti-HIV agent.
17. A composition according to claim 16 wherein the anti-STD agent is N-9.
18. A composition according to claim 17 wherein the polymer is polycarbophil.
19. A composition according to claim 18 wherein the intended use of the composition is vaginal application.
20. A composition according to claim 19 wherein a single dose of the composition contains about 52.5 mg. of N-9, which dose is provided with or in a single- or multi-dose disposable applicator.
21. An anti-STD bioadhesive composition comprising a cross-linked polycarboxylic acid polymer formulation.
22. A bioadhesive drug delivery composition comprising a cross-linked polycarboxylic acid polymer and nonoxynol-9 formulation.
23. A method of delivering an anti-STD agent to a subject comprising inserting a bioadhesive cross-linked polycarboxylic acid polymer formulation with the anti-STD agent into a body cavity in an amount sufficient to demonstrate anti-STD activity without significant causation of irritation to the local epithelial tissues.

24. A method according to claim 23 wherein the polymer is polycarbophil.
25. A method according to claim 23 wherein the formulation includes at least one adjuvant.
26. A method according to claim 23 wherein the anti-STD agent is an anti-HIV agent.
- 5 27. A method according to claim 23 wherein the subject is a female.
28. A method according to claim 27 wherein the body cavity is the vagina.
29. A method according to claim 28 wherein the anti-STD agent is an anti-HIV agent.
30. A method according to claim 29 wherein the anti-STD agent is nonoxynol-9.
31. A method according to claim 30 wherein the polymer is polycarbophil.
- 10 32. A method according to claim 31 wherein about 52.5 mg. of N-9 is inserted into the vagina.
33. A method according to claim 32 wherein the formulation includes at least one adjuvant.
34. A method according to claim 33 wherein the formulation is a gel-like product which
15 is provided with or in a single- or multi-dose disposable applicator.

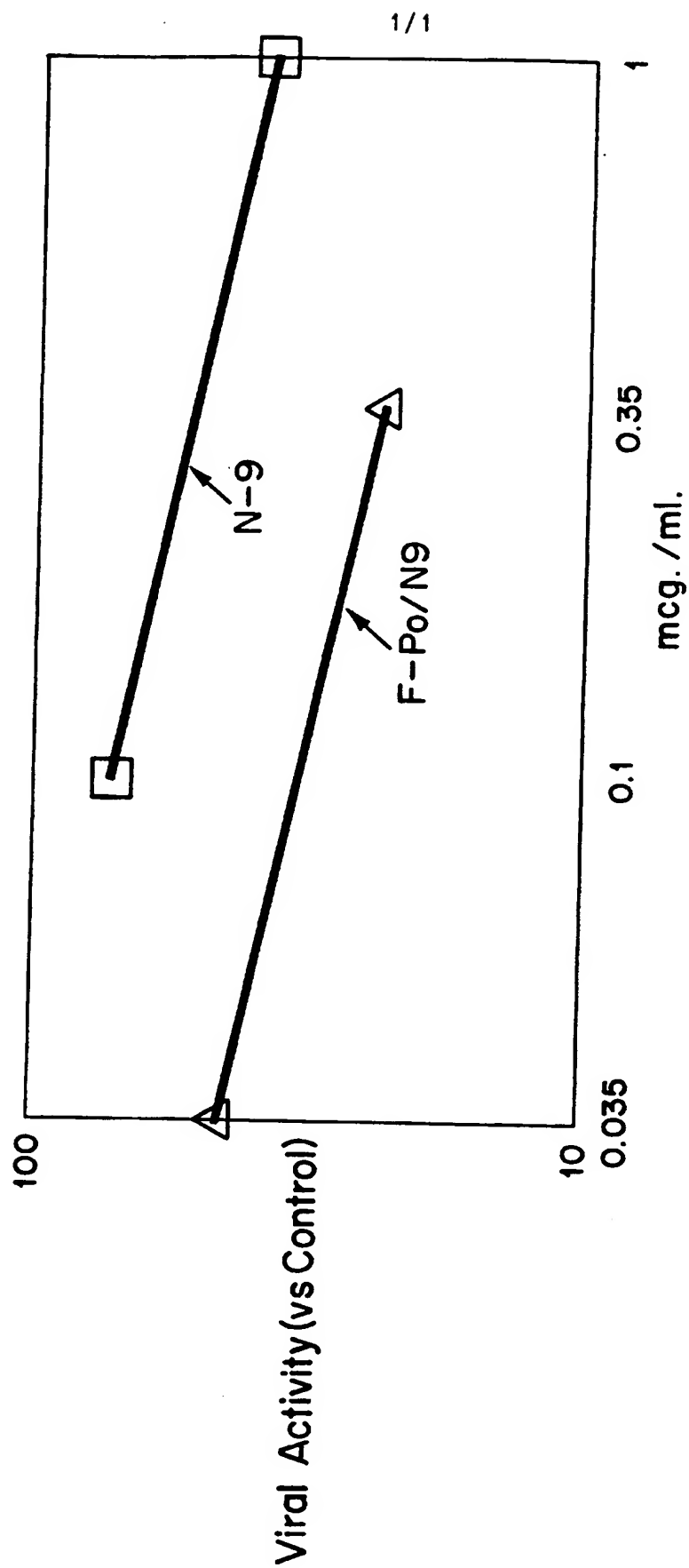


FIG. 1

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 95/13424

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K47/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 077 063 (VIRAL GENETICS INC.,U.S.A.) 20 April 1983 see claims 1,6,9,10 see page 1, line 31 - line 38 see page 15, line 18 see page 16, line 5 - line 16 ---	1,3,5,8, 10,12
A	WO,A,91 06283 (COLUMBIA LABORATORIES INC.,U.S.A.) 16 May 1991 cited in the application see claims ---	1,2,5,19
A	EP,A,0 351 301 (SOCIETE ANONYME SSPL SAFE SEX PRODUCTS LICENSING,FR) 17 January 1990 see the whole document ---	1,5,8, 12,19
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

29 February 1996

Date of mailing of the international search report

7.03.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Scarponi, U

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/13424

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 385 030 (H.H.LEVEEN ET AL.) 5 September 1990 see claims 1,3,4,7 -----	1,5,8, 10,12,19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 95/13424

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-77063	20-04-83	CA-A- 1190148	09-07-85
		DE-A- 3278234	21-04-88
		EP-A- 0305551	08-03-89
		JP-C- 1777472	28-07-93
		JP-A- 58077824	11-05-83
		JP-B- 63065050	14-12-88
		US-A- 4507281	26-03-85
		US-A- 4957734	18-09-90

WO-A-9106283	16-05-91	AT-T- 113841	15-11-94
		AU-B- 639069	15-07-93
		AU-B- 7033191	31-05-91
		CA-A- 2072148	01-05-91
		DE-D- 69014081	15-12-94
		EP-A- 0431719	12-06-91
		EP-A- 0500807	02-09-92
		ES-T- 2050096	16-05-94
		HU-A- 68635	28-07-95
		IE-B- 62386	25-01-95
		IL-A- 96148	31-08-95
		JP-T- 5504338	08-07-93
		US-A- 5474768	12-12-95
		AT-T- 112157	15-10-94
		DE-D- 69012955	03-11-94
		DE-T- 69012955	09-02-95
		EP-A- 0429156	29-05-91
		ES-T- 2059300	16-11-94
		US-A- 5188826	23-02-93

EP-A-351301	17-01-90	AP-A- 108	23-02-91
		AU-B- 625716	16-07-92
		AU-B- 3802689	11-01-90
		CZ-A- 8904238	13-12-95
		DE-D- 68910892	05-01-94
		DE-T- 68910892	05-05-94
		ES-T- 2062065	16-12-94
		HK-A- 131095	24-08-95
		HR-A- 921074	30-06-95
		IE-B- 63115	22-03-95
		IL-A- 90910	29-12-94

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 95/ 13424

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 23-34 are directed to a method of treatment of the human body by therapy (Rule 39.1(iv)PCT), the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 95/13424

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-351301		JP-A- 2167235	27-06-90
		JP-B- 7074164	09-08-95
		LT-A- 1660	25-07-95
		LV-B- 10573	20-08-95
		OA-A- 9123	31-10-91
		PL-B- 161848	31-08-93
		PT-B- 91108	31-01-95
		US-A- 5439685	08-08-95

EP-A-385030	05-09-90	US-A- 5000749	19-03-91
		CA-A- 2003952	02-09-90
		DE-D- 68910106	25-11-93
		DE-T- 68910106	03-03-94
		US-A- 5070889	10-12-91
		US-A- 5156164	20-10-92
